IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	Gao, D. *et al.*	ATTORNEY DOCKET NO.:	C-3169-1-US
SERIAL NO.:	09/451,641	GROUP ART UNIT:	1615
FILED:	November 30, 1999	EXAMINER:	S. Tran
TITLE:	CELECOXIB COMPOSITIONS		
DATE:	January 2, 2003		

CERTIFICATE OF MAILING

I hereby certify that this communication and its recited enclosures are being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on January 2, 2003.

Susan B. Gaulik

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

PETITION FOR EXTENSION OF TIME

Applicant hereby makes petition for extension of time of three months for response to the Office Action dated July 3, 2002 in the above-referenced application. A shortened statutory period of three months was set in that Office Action. In connection with this petition, please charge $920.00 or the sum required under 37 C.F.R. §1.17(a)(3) to Deposit Account No. 19-1025.

COMMENTS ON INTERVIEW ON DECEMBER 10, 2002

Applicant appreciates the courtesy shown to the undersigned by Examiner Tran in a personal interview in the present matter on December 10, 2002. Applicant agrees that the Interview Summary prepared by the Examiner is an accurate record of the substance of the interview but, as more specifically indicated below, respectfully disagrees with the Examiner's position expressed therein with regard to obviousness of the present invention over Black (European Patent No. 0 863 134).

During the interview Applicant's agent expressed willingness to advance prosecution by proposing certain amendments to the claims, for example by conforming Claim 1

substantially to Claims 1 or 2 as granted in the counterpart application at EPO (European Patent No. 1 049 467, copy attached). Such an amendment, which would introduce a requirement for celecoxib particle size having a D_{90} less than 200 mm, is not proposed herein, as at the close of the interview it remained unclear as to whether amendment in this fashion would overcome the present rejection. However, it is noted that Black is silent as to particle size of his subject compound when formulated as a discrete orally deliverable solid dosage form.

The Examiner indicates in the Interview Summary that she will contact the undersigned upon review of Applicant's remarks herein and further review of Black, with a view to considering suggestions for putting the present application in condition for allowance.

RESPONSE TO OFFICE ACTION DATED JULY 3, 2002

Claims 1-50 and 76-94 are pending in the present Application.

1. Rejection under 35 U.S.C. § 103 over Black

Claims 1-50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Black (European Patent No. 0 836 134). This rejection is respectfully traversed. The Examiner indicates (Office Action, page 5) that Applicant's previous arguments "have been fully considered but they are not persuasive" and that the original 103(a) rejection is maintained.

1.1. A *prima facie* case of obviousness has not been made

The Examiner is respectfully referred to Applicant's previous response accompanying the Request for Continued Examination dated October 17, 2001, as expanded below.

M.P.E.P § 2143 sets out three basic criteria for establishing a *prima facie* case of obviousness. If any one of the three criteria is satisfied the *prima facie* case fails, yet not one of these criteria is satisfied in the present rejection.

First, there is no suggestion, either in Black or in generally available knowledge at the time of the present invention, to modify the reference. Applicant admits that celecoxib is a compound having similar utility (a selective COX-2 inhibitory drug) to Black's compound, but does not agree that Black's compound is a "derivative of celecoxib" as suggested in the Interview Summary of December 10, 2002. The prior art "must suggest the desirability of the claimed invention". M.P.E.P. § 2143.01; see in particular *In re Fine*, 837 F.2d 1071 (Fed. Cir. 1988). Black fails to suggest the property, namely high relative bioavailability by comparison with an orally administered solution of the drug, that makes the present invention so desirable.

Second, there was, at the time of the present invention, no reasonable expectation of

success in formulating celecoxib, an extraordinarily insoluble compound, as a discrete solid dosage form having high relative bioavailability. Indeed textbook teaching predicted such a dosage form would have low relative bioavailability. The quotation from Remington: The Science and Practice of Pharmacy drawn to the Examiner's attention in Applicant's response of October 17, 2001 is repeated herein because of its particular pertinence:

> A drug usually has the highest bioavailability if administered orally as an aqueous solution; finely comminuted drugs in suspension follow closely. However, as a drug is packed into hard gelatin capsules or compacted into tablets, its bioavailability decreases.

Third, all claim limitations are not taught or suggested in the cited art. The Examiner agrees (Office Action, page 3) that Black is silent as to the teaching of celecoxib. Furthermore, there is no teaching or suggestion in Black of relative bioavailability not less than about 50% by comparison with an orally administered solution.

The Examiner has suggested the relative bioavailability property is "inherent" (Interview Summary of December 10, 2002), absent a showing by Applicant that "the powder or granule formulation of Black does not have the bioavailability rate of 50% or more" (Office Action, page 6), and shifts the burden to Applicant to make such a showing. This shifting of the burden is improper, as previously submitted and as further demonstrated (Section 1.2) below.

The interview on December 10, 2002 was useful in clarifying for Applicant that the present 103(a) rejection is founded on a property asserted by Examiner to be inherent in Black. Applicant notes M.P.E.P. § 2112: "The ... inherent disclosures of a prior art reference may be relied upon in the rejection of claims under 35 U.S.C. 102 or 103." Applicant also notes citation therein of *In re Napier*, 55 F.3d 610 (Fed. Cir. 1995), a case affirming a 103 rejection based in part on an inherent disclosure. In making the proposition that the inherent teaching of a prior art reference can arise in the context of obviousness as well as anticipation, *In re Napier* (as well as M.P.E.P. § 2112) cites *In re Grasselli*, 713 F.2d 731 (Fed. Cir. 1983). Interestingly, however, the court in *In re Grasselli* found that if the evidence of record fails to establish a property of prior art as inherent, "obviousness cannot be predicated on that which is unknown". See also *Ex parte Schricker*, 56 U.S.P.Q.2d (BNA) 1723 (Board of Patent Appeals and Interferences 2000): "Inherency and obviousness are somewhat like oil and water they do not mix well."

The fact situation here corresponds to that of *In re Grasselli* (where an inherent

property of prior art is unknown) rather than to that of *In re Napier* (where it was possible to ascertain an inherent prior art property from other publicly available information). High relative bioavailability is not a known or inevitable property of Black's discrete solid dosage forms containing his Compound A, based on evidence known to Applicant or adduced by the Examiner. (In this regard it is respectfully noted that bioavailability of a powder or granule formulation of Black's compound, even if known, would not be relevant to the present claims that require discrete solid dosage forms.) Thus the Examiner improperly predicates obviousness on that which is unknown. *In re Grasselli.*

In support of the argument that a *prima facie* case has been made, the Examiner proposes that "... Black obtained the same result desired by the applicant, *e.g.*, controlled release, or sustained release composition having the half-li[f]e over 24 hour period ..." (Office Action, pages 5–6). It is respectfully pointed out that half-life is not a property recited in Claim 1 as now before the Examiner, nor does it bear any relation to the particular advantage noted for the present invention, namely high relative bioavailability. Furthermore, the present invention relates not to controlled release or sustained release compositions but to "superior immediate release compositions capable of providing rapid relief from a cyclooxygenase-2 mediated disorder" (Specification, page 5 lines 22–23), the strong clinical benefits of such compositions resulting from "improved bioavailability of celecoxib" (Specification, page 5, lines 25–26).

It is respectfully submitted, therefore, that the Examiner has failed to satisfy at least one of the M.P.E.P. § 2143 criteria (indeed has satisfied none of the three) and that a *prima facie* case of obviousness has not been made.

1.2. The burden to show nonobviousness over Black is improperly shifted to Applicant

The burden placed on Applicant "to establish that the powder or granule formulation of Black does not have the bioavailability rate of 50% or more" is clearly improper in absence of a sustainable *prima facie* case of obviousness. In attempting to make a case for the shifting of the burden, the Examiner relies on *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). Applicant respectfully submits that *In re Brana* relates to a question of utility under 35 U.S.C. § 101/112 as opposed to one of nonobviousness under 35 U.S.C. § 103 and is not on point. Furthermore, to the extent *In re Brana* is of relevance in the present context, the mere assertion by the Examiner that high relative bioavailability is an inherent property of Black's compositions does not constitute evidence as required by *In re Brana* for a shifting of burden

to Applicant to rebut.

The Examiner's attention is respectfully drawn to M.P.E.P. § 2112: "Once a reference teaching product appearing to be substantially identical is made the basis of a rejection, and the Examiner presents evidence or reasoning tending to show inherency, the burden shifts to the Applicant to show an unobvious difference." No such evidence or reasoning has been presented. The Examiner's observation (Interview Summary) that "Black teaches the derivative of celecoxib [for which read a compound having similar utility to celecoxib] for the same treatment and in the same dosage form" is insufficient basis on which to conclude that high relative bioavailability is inherent in Black. Again, mere assertion of inherency is an improper basis for shifting the burden to Applicant under M.P.E.P. § 2112.

1.3. Even if a *prima facie* case of obviousness were made, evidence exists to rebut it

As will be clear from Applicant's submission hereinabove, it is not admitted herein that a *prima facie* case of obviousness has been shown. However, even if, *arguendo*, such a case could be sustained, it is rebuttable at least for the reason that prior art teaches away from the present invention. M.P.E.P. § 2145, X, *D*, 3, first paragraph. Standard textbook teaching (Ansel, cited in Applicant's previous response) predicts that celecoxib, a practically insoluble drug and one having low absolute bioavailability when unformulated, would be poorly absorbed if orally administered as particulate material in a solid dosage form, and would therefore show low relative bioavailability by comparison with the same dose of celecoxib orally administered in solution in a suitable solvent. Contrary to the Ansel prediction, relative bioavailabilities of 50% or greater have been found by the present inventors when celecoxib is formulated according to the invention.

In the interview on December 10, 2002, the Examiner suggested submission of data showing an unexpected result of the claimed composition having a drug particle size as recited in the granted EP claims.

The Examiner's attention is first respectfully drawn to Example 13 of the present specification (pages 53 -54). D_{90} particle size of celecoxib used in the discrete solid dosage forms of Example 13 is less than about 37 μm (sentence bridging pages 53 and 54). A 100 mg celecoxib capsule having this D_{90} particle size is shown in Table 13B (page 54) to have AUC similar to a suspension in apple juice, based on a pharmacokinetic study in 10 adult subjects. As a fine suspension has been shown to have a relative bioavailability close to 100% (compare compositions D (suspension) and E (solution) in Tables 11-2C and D at page 50), suggesting

that a fine suspension can be used as a "surrogate" for a solution, the 100 mg capsule of Example 13 can be concluded to have a relative bioavailability that is likewise close to 100%. This is a truly unexpected result, made all the more surprising in view of the fact that the capsule in question contained no wetting agent such as polysorbate 80 or sodium lauryl sulfate. (Wetting agent is a preferred but not required component of compositions of the present invention.)

The Examiner's attention is further drawn to Example 18 of the present specification (pages 61–63). In a pharmacokinetic study in 36 adult subjects, a celecoxib composition similar to the 100 mg capsule of Example 13 (and having similar particle size, the celecoxib having been milled through a 40 mesh oscillating screen) was compared, in a total dose of 200 mg, to a 200 mg capsule and a fine suspension in apple juice. Again, AUC relative to the fine suspension was unexpectedly high both for the 100 mg capsule (containing no wetting agent) and for the 200 mg capsule (containing 3% sodium lauryl sulfate). To the extent that the fine suspension is a "surrogate" for a solution, the AUC_{0-t} results shown in Table 18B (page 63) correspond to a relative bioavailability of about 95% for the 100 mg capsule and about 98% for the 200 mg capsule.

Other grounds for rebuttal have already been set forth in previous responses by Applicant. These grounds are maintained by Applicant and need not be repeated here.

Withdrawal of the rejection of Claims 1–50 under 35 U.S.C. § 103(a) as unpatentable over Black is therefore respectfully requested.

2. Rejection under 35 U.S.C. § 103 over Black and Jain in view of Plachetka

Claims 1–50 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Black (European Patent No. 0 836 134) and Jain (U.S. Patent No. 6,165,506) in view of Plachetka (U.S. Patent No. 6,077,539). This rejection is respectfully traversed.

Jain adds no element of Claim 1 of the present application that is not present in Black. Jain is cited for the disclosure of wetting agent, which as pointed out above is not an essential feature of the present invention. Jain's drug is naproxen, which is not a selective COX-2 inhibitor and which, unlike celecoxib, is poorly soluble only in an acid medium. Furthermore, naproxen is a compound having high absolute bioavailability (95%; see PDR 56th ed. (2002), page 2968, copy attached). As shown in Table 11-2C and D (page 50 of the present specification), absolute bioavailability of celecoxib is only 16.9% when administered in unformulated composition F, and rises, at best, to 75.9% (average of female and male dogs)

when administered as an oral solution. Thus celecoxib is a compound with intrinsically low bioavailability, and one of ordinary skill in the art would not have been motivated to formulate such a drug as a discrete solid dosage form based on the teaching of Jain (that relates to a drug of high absolute bioavailability) in combination with the other cited references, with the expectation of achieving high relative bioavailability as obtained by the present inventors.

Plachetka likewise adds no element of Claim 1 of the present application that is not present in Black. Plachetka is cited for the disclosure of wetting agent and long half-life (neither of which is a recited element in Claim 1 as now before the Examiner). Plachetka discloses several drugs including oxaprozin, which is not a selective COX-2 inhibitor and, although of very low solubility in water, is nonetheless eight times more soluble than celecoxib. As shown in the attached MSDS (material safety data sheet), oxaprozin has a solubility of 0.004% (40 ppm). Celecoxib, by contrast, has a solubility of only 5 ppm. Furthermore, oxaprozin is a compound of high absolute bioavailability (95%, as admitted in the present Office Action at page 4, 2nd paragraph). One of ordinary skill in the art would not have been motivated to formulate a drug of intrinsically low bioavailability such as celecoxib as a discrete solid dosage form based on the teaching of Plachetka in combination with the other cited references, with the expectation of achieving high relative bioavailability as obtained by the present inventors.

Applicant respectfully submits that a *prima facie* case of obviousness under M.P.E.P. § 2143 has not been made, at least for the following reasons.

- No motivation exists to combine Jain and/or Plachetka with Black. Jain's and Plachetka's compounds are not selective COX-2 inhibitors and, unlike celecoxib, have very high absolute bioavailability, therefore are not pertinent to the problem faced by the present inventors.
- No reasonable expectation of success attended formulation of celecoxib in a discrete solid oral dosage form; indeed, as pointed out above, textbook teaching predicted low relative bioavailability for such a dosage form.
- All claim limitations are not taught or suggested by the combination of references cited. Specifically, no teaching or suggestion, explicit or inherent, can be found in any of the cited references of (a) celecoxib or (b) a solid dosage form having a relative bioavailability not less than about 50% by comparison with an orally administered solution.

Withdrawal of the rejection of Claims 1–50 under 35 U.S.C. § 103(a) as unpatentable over Black and Jain in view of Plachetka is therefore respectfully requested.

3. Rejection under 35 U.S.C. § 103 over Black, Plachetka and Liversidge

Claims 76–94 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Black (European Patent No. 0 836 134), Plachetka (U.S. Patent No. 6,077,539) and Liversidge (U.S. Patent No. 5,552,160. This rejection is respectfully traversed.

It appears the Examiner has treated all of Claims 76–94 as process claims in making the present rejection. Applicant respectfully points out that while Claims 76–83 and 91–94 are indeed drawn to a process, Claims 84–90 are composition claims. Of these composition claims, Claims 85–90, but not Claim 84, recite various particle size limitations.

3.1. Composition claims

With respect to Claim 84, which is dependent from Claim 1, the combination of Black and Plachetka does not provide evidence of *prima facie* obviousness as shown in Section 2 above, and Liversidge does not add any teaching or suggestion of pertinence to the specific limitation of Claim 84, namely a relative bioavailability not less than about 70%. If Claim 1 is nonobvious under 35 U.S.C. § 103, all claims dependent therefrom are allowable. M.P.E.P. § 2143.03.

With respect to Claims 85–90, each of which is dependent from Claim 1, Liversidge teaches particle size reduction of an NSAID such as naproxen to less than about 400 nm (0.4 μm) (see Liversidge, abstract). Liversidge also discloses, as a control composition, naproxen having a particle size of 20–30 μm (column 7 lines 35–39). No information is provided on bioavailability relative to orally administered solution, but it is noted that the 20–30 μm particles exhibited an AUC of 15,228 μg.min/ml, which was distinctly suboptimal by comparison with the AUC of 19,062 μg.min ml exhibited by 240–300 nm (0.24–0.3 μm) particles. See table at top of column 9. It is further noted that the naproxen particles administered by Liversidge were in the form of a suspension, not a discrete solid dosage form. The examiner notes disclosure by Liversidge of particles "preferably having size less than 100 μm", but this is in the context of "a conventional coarse form" of the drug (column 4, line 48) that is to be subjected to further particle size reduction. Liversidge therefore stresses the importance of reducing particle size to extremely small dimensions, and provides no suggestion that particles up to 200 μm in size (present Claim 85) or in any of the narrower ranges cited (present Claims 86–90) would be worth evaluating.

Furthermore, Liversidge adds no element of Claim 1 not already present in Black or Plachetka. If Claim 1 is nonobvious under 35 U.S.C. § 103, all claims dependent therefrom are allowable. M.P.E.P. § 2143.03. Withdrawal of the rejection of Claims 84–90 under 35 U.S.C. § 103(a) as unpatentable over Black, Plachetka and Liversidge is therefore respectfully requested.

3.2. Process claims

With respect to Claims 76–83 and 91–94, which are process claims, it is noted first that Claims 76 and 94 recite no particle size reduction step. Claim 76 was previously found allowable if rewritten in independent form (Office Action dated August 31, 2001). Nothing in Plachetka or Liversidge can be found to change this conclusion. Claim 94 depends from Claim 76 and should similarly be allowable.

With respect to Claims 77–83 and 91–93, each of which recites a particle size reduction (milling) step, the Examiner admits that Black and Plachetka are silent as to the process of reducing particle size, and cites Liversidge for the milling step. As pointed out in Section 3.1 above, Liversidge stresses the importance of reducing particle size to extremely small dimensions, and provides no suggestion that milling only to 200 μm in size (present Claim 77) or to any of the narrower ranges cited (present Claims 78–80), regardless of how performed, would be worth trying. Furthermore, each of Claims 77–83 and 91–93 is dependent from Claim 76 and incorporates all the limitations of Claim 76. If Claim 76 (when rewritten in independent form) is nonobvious under 35 U.S.C. § 103, all claims dependent therefrom are allowable. M.P.E.P. § 2143.03.

Withdrawal of the rejection of Claims 76–83 and 91–94 under 35 U.S.C. § 103(a) as unpatentable over Black, Plachetka and Liversidge is therefore respectfully requested.

All claims presently in consideration are believed to be in condition for allowance. However, the Examiner is requested to call the undersigned, as agreed in the Interview on December 10, 2002, should further amendment be found necessary.

Respectfully submitted,

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Attachments
Fee transmittal form
European Patent No. 1 049 467 (counterpart of the present application)
Copy of PDR 56th ed. (2002), page 2968
Copy of oxaprozin MSDS